

REMARKS

In the Office Action dated May 2, 2006, the Examiner has set forth a requirement for restriction under 35 U.S.C. §121, alleging that the subject matter defined by the claims of the present invention represents the following five separate and distinct inventions:

- | | |
|-----------|--|
| Group I | Claims 1-27 are drawn to a genetically engineered methylotropic yeast strain transformed with a nucleotide sequence coding for a glycoprotein to produces a glycoprotein having a mammalian-like N-glycan structure modified to expresses (1) an α -1, 2-mannosidase or a functional part thereof, (2) an N-acetylglucosaminyltransferase I (or GnTI) or a functional part thereof, and (3) a β -1, 4-galactosyltransferase (GalT) or a functional part thereof, and wherein the genomic OCHI gene in the modified strain is inactivated classified in class 435, subclass 254.11. |
| Group II | Claims 28, 29, 31 and 32 are drawn to a method of recombinantly producing a glycoprotein having a mammalian-like N-glycan structure in a methylotrophic yeast strain, comprising transforming said strain with a nucleotide sequence coding for said glycoprotein; modifying said strain such that the modified strain expresses (1) an α -1, 2-mannosidase or a functional part thereof, (2) an N-acetylglucosaminyltransferase I (or GnTI) or a functional part thereof, and (3) a β -1, 4-galactosyltransferase (GalT) or a functional part thereof, and wherein the genomic OCHI gene in the modified strain is inactivated; and producing said glycoprotein in the modified stain. Classified in class 435, subclass 69.1. |
| Group III | Claims 30 and 33 are drawn to a glycoprotein produced in a methylotrophic yeast strain having a mammalian-like N-glycan structure, classified in class 530, subclass 395. |
| Group IV | Claim 34 is drawn to vector comprising a nucleotide sequence coding a galT, operably linked to a promoter sequence and a 3' termination sequence, wherein said promoter sequence and said 3' termination sequence are functional in a methylotrophic yeast stain to achieve expression of said GalT in said stain classified in class, 435, subclass 320.1. |

Group V Claims 35 and 38 are drawn to a kit comprising (1) a vector comprising a nucleotide sequence coding for an α -1, 2-mannosidase or a functional part thereof, (2) a vector comprising an N-acetylglucosaminyltransferase I (or GnTI) or a functional part thereof, and (3) a vector comprising a β -1, 4-galactosyltransferase (GalT) or a functional part thereof wherein each of the vectors is capable of directing the expression of the encoded protein further comprising a gene capable of disrupting the genomic OCHI gene further comprising a vector encoding a glycoprotein heterologous to said methylotrophic strain in a methylotrophic strain and the methylotrophic strain classified in class 435, subclass 6.

Further, the Examiner states that in the event that Group I is elected, Applicants must also elect the specific origin of the methylotrophic yeast strain from (a) *Candida*, (b) *Hansunella*, (c) *Torulopsis* or (d) *Pichia*. Furthermore, Applicants must elect the origin for each of the enzymes ((1) α -1, 2-mannosidase, (2) N-acetylglucosaminyltransferase I (or GnTI) and (3) the β -1, 4-galactosyltransferase (GalT) from the following species: (i) human, (ii) rabbit, (iii) rat, (iv) plant, (v) insect, (vi) nematode, (vii) protozoa, (viii) *Aspergillus*, (ix) *Trichoderma reesei*.

In order to be fully responsive to the Examiner's requirement for restriction, Applicants provisionally elect to prosecute the subject matter of Group I, Claims 1-27. In connection with the species election, Applicants elect *Pichia* as the species of the methylotrophic yeast strain. Further, Applicants elect "*Trichoderma reesei*" for α -1, 2-mannosidase, "human" for GnTI, and "human" for GalT. Applicants reserve the right to file one or more divisional applications directed to the non-elected subject matter in this application. However, pursuant to 37 C.F.R. §§ 1.111 and 1.143, Applicants hereby traverse the Examiner's requirement for restriction and requests reconsideration thereof in view of the following remarks.

An Examiner's authority to require restriction is defined and limited by statute:

If two or more independent and distinct inventions are claimed in one application, the Commissioner may require the application to be restricted to one of the inventions.

35 U.S.C. § 121, first sentence (emphasis added). The implementing regulations of the Patent and Trademark Office include the mandate that restriction is appropriate only in cases presenting inventions which are both independent and distinct, 37 C.F.R. §§1.141-142. Without a showing of independence and distinctness, a restriction requirement is unauthorized. In the present application, the claims which the Examiner has grouped separately are not "independent and distinct" so as to justify the restriction requirement.

The Examiner acknowledges that Groups I and II are related as product and process of use. However, citing MPEP § 806.05(h), the Examiner contends that Groups I and II are distinct inventions, because the methylotrophic yeast of Group I can be used to produce the various enzymes, instead of the glycoproteins as claimed in Group II. Similarly, the Examiner admits that Groups II and III are related as process of making and product made. However, citing MPEP § 806.05(f), the Examiner contends that Groups II and III are distinct inventions, allegedly because the glycoproteins of Group III can be chemically synthesized (independent of the methods of Group II), and the methods of Group II can be used to produce other products such as the three enzymes (α -1, 2-mannosidase, GnTI, and Ga1T), instead of the glycoproteins of Group III.

Applicants respectfully submit that the methylotrophic yeast of Group I is genetically engineered in a way such that the various enzymes are targeted to certain intracellular location to exert their enzymatic activities for the production of glycoproteins having a mammalian-like N-glycan structure. In light of the specification and the claim language, the methylotrophic yeast of Group I is clearly not designed for the production of the various enzymes themselves. Similarly,

the methods of Group II, which employs the methylotrophic yeast of Group I, are also not designed for the production of the enzymes. Rather, the methods are specifically directed to the production of the glycoproteins of Group III. Therefore, Groups I, II and III are clearly related to each other, and are not "independent and distinct".

The Examiner also alleges that Group I is unrelated to Group IV, because Group IV is drawn to a vector comprising a single gene encoding a GalT which, in the Examiner's opinion, is unrelated to the genetically engineered methylotrophic yeast strain of Group I, which is transformed with various constructs for the production of a glycoprotein having a mammalian-like N-glycan structure.

Applicants respectfully submit, however, that it is abundantly clear that the vector of Group IV can be used in the genetic engineering process to make the strain of Group I, even though additional vectors may be used to complete the genetic engineering process.

Applicants further submit that the interdependence of Groups I-V is confirmed -- indeed, it is mandated-- by virtue of the fact that 35 U.S.C. §112 compels disclosure of all aspects of the invention in the one application which applicants have filed. For example, an application claiming the genetically engineered strains (Group I) is required to disclose inter alia how to make and use that invention. In other words, a description of the means and method for making (e.g., the vectors of Group IV and the kits of Group V) and using (the methods of Group II) the subject strains is a mandatory part of the application directed to the strains. Indeed, if any of these aspects of a complete disclosure were omitted, the application could be considered defective under §112, first paragraph. Consequently, it is clear that aspects of a given invention, such as a product, its use, and the process of producing that product, are necessarily interdependent, not independent, from each other.

Applicants further respectfully submit that Groups I-V are all related as different aspects of a single invention. The courts have recognized that it is in the public interest to permit applicant to claim several aspects of their invention together in one application, as the applicant have done herein. The CCPA has observed:

We believe the constitutional purpose of the patent system is promoted by encouraging applicants to claim, and therefore to describe in the manner required by 35 U.S.C. §112 all aspects as to what they regard as their invention, regardless of the number of statutory classes involved.

In re Kuehl, 456 F.2d 658, 666, 117 U.S.P.Q. 250, 256 (CCPA 1973). This interest is consistent with the practical reality that a sufficiently detailed disclosure supporting claims to one aspect of an invention customarily is sufficient to support claims in the same application to other aspects of the invention.

As to the species election, Applicants respectfully submit that although the enzymes from different species have different nucleotide and amino acid sequences, the enzymes have essentially the same type of enzymatic activity suitable for use in the present invention.

It is vital to all applicant's that restriction requirements issue only with the proper statutory authorization, because patents issuing on divisional applications which are filed to prosecute claims that the Examiner held to be independent and distinct can be vulnerable to legal challenges alleging double patenting. The third sentence of 35 U.S.C. §121, which states that a patent issuing on a parent application "shall not be used as a reference" against a divisional application or a patent issued thereon, does not provide comfort to applicant's against such allegations. The Court of Appeals for the Federal Circuit has declined to hold that § 121 protects a patentee from an allegation of same-invention double patenting, Studiengesellschaft Kohle GmbH v. Northern Petrochemical Co., 784 F.2d 351, 355, 288 U.S.P.Q. 837, 840 (Fed. Cir.

1986). In Gerber Garment Technology Inc. v. Lectra Systems Inc., 916 F.2d 683, 16 U.S.P.Q. 2d 1436 (Fed. Cir. 1990), the court held that §121 does not insulate a patentee from an allegation of "obviousness-type" double patenting, and in fact affirmed the invalidation on double patenting grounds of a patent that had issued from a divisional application filed following a restriction requirement. Furthermore, it is far from clear that the step of filing a terminal disclaimer is available to resolve a double patenting issue that arises after the issuance of a patent on the divisional application.

All these considerations indicate that the imposition of a restriction requirement with inadequate authority can lead to situations in which an applicant's legitimate patent rights are exposed to uncertainty and even extinguished. Accordingly, to protect a patentee's rights and to serve the public interest in the legitimacy of issued patents, Applicants respectfully urge the Examiner not to require restriction in cases such as the present application wherein various aspects in a unitary invention are claimed.

Finally, Applicants respectfully submit that a determination to make the pending restriction requirement final must evidence the patentable distinctness of the defined five groups and species, one from the other, as presented by the Examiner.

Applicants acknowledge that withdrawn process claims that depend from or otherwise include all the limitations of an allowable product claim will be rejoined.

In view of the foregoing comments, it is respectfully urged that the Examiner reconsider and withdraw the requirement for restriction and provide an action on the merits with respect to all the claims.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Xiaochun Zhu', written in a cursive style.

Xiaochun Zhu

Registration No. 56,311

SCULLY, SCOTT, MURPHY & PRESSER, P. C.
400 Garden City Plaza-STE 300
Garden City, New York 11530
(516) 742-4343
XZ:ab